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Applicant's arguments filed February 4, 2008 have been fully considered but they are not persuasive. Claims 87 and 89-100 are pending.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 87-97 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of copending Application No. 10/969,646 for reasons set forth in the office action mailed February 9, 2007.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant states a terminal disclaimer will be filed when allowable subject matter is indicated.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 87, 89-96, 99 and 100 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a method for reprogramming a non-human animal somatic cell nucleus, comprising incubating said nucleus with a CSF extract of an MII egg followed by incubation of the somatic cell nucleus in a cytoplasmic extract of an induced egg, wherein said somatic cell nucleus is reprogrammed as indicated by nuclear swelling, nucleic acid replication and entry into mitosis, wherein said nucleus and said cell are of the same species;

a method for activating a somatic cell nucleus comprising incubating a somatic cell nucleus with the an CSF extract of a MII egg followed by incubation with an extract of an egg just prior to S-phase to yield an activated nucleus as indicated by nuclear swelling, nucleic acid replication and entrance into mitosis; and

a method of reprogramming a nucleus of a somatic cell to bring about nuclear activation comprising pretreating said nucleus to release said nucleus from surrounding cytoskeleton, incubating said pretreated nucleus with a CSF extract of an MII egg followed by incubation of said nucleus with an induced egg extract to activate said nucleus indicated by nuclear swelling, nucleic acid replication and entrance into mitosis,

does not reasonably provide enablement for incubation of a nucleus in an MII or induced egg, development of an embryo and indicators of activation other than nucleus swelling, nucleic acid replication and entry into mitosis for reasons set forth in the office action mailed August 2, 2007. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 87, 89-96, 99 and 100 are not enabled for their full breadth as the specification fails to provide guidance for the claims as written. The specification teaches a method of reprogramming a somatic cells, as indicated by the somatic cell nucleus

undergoing nuclear swelling, nucleic acid replication an entry into mitosis, by incubating a somatic cell nucleus in an "activating" cell extract produced from activated Xenopus oocytes prepared as disclose (specification, page 25). The method further incubates the activated nucleic in an extract prepared from MII-arrested Xenopus eggs, the extract containing a cytostatic factor for reprogramming the nucleic (specification, page 35, line 23).From the specification, the disclosed method critically requires both incubations for reprogramming, which is measured by the nucleus' undergoing nuclear swelling, nucleic acid replication and entry into mitosis.

Applicant argues the specification discloses the production of egg extracts prepared from the cytoplasm of non-induced eggs arrested in meiotic metaphase II (CSF extracts) and from the cytoplasm of induced eggs (activated egg extracts). Applicant argues the skilled artisan at the time of filing would understand that exposure of somatic cell nuclei to these extracts is the equivalent of exposing the nuclei to the cytoplasm of intact eggs. Applicant argues the cytoplasm from MII eggs have the same factors that trigger chromatin condensation and nuclear membrane breakdown. Applicant argues the specification clearly defines the stage of the cell cycle an oocyte cytoplasm required for activation. Applicant argues further it is easy to screen for a reprogrammed cell by looking at the cellular replication that occurs because the nucleus is transplanted from one cell to another. Applicant argues the demonstration of nuclear swelling, complete nucleic acid replication and entry into mitosis of somatic cells incubated in Xenopus egg CSF extract followed by incubation in an activating egg extract is sufficient evidence for the production of a multicellular embryo. Applicant argues the complete genome replication cannot occur in the absence of eliminating DNA methylation patterns. Applicant argues therefore the complete replication of the somatic cell genome means the cell has been successfully reprogrammed. These arguments are not persuasive.

The claims are not enabled simply because the specification does not disclose exposure to egg cytoplasm within an intact egg as a means to reprogram a somatic cell. At each place in the specification, where the cell cycle stage of the eggs is discussed, it is with reference to producing an egg extract. A reading of the specification would indicate an intact egg would not be sufficient for reprogramming. Further, reprogramming can only be indicated by the production of a live offspring (Campbell, page 250, col. 1, parag. 2, lines 1-2). The present method shows only chromosome condensation, nuclear membrane breakdown and DNA synthesis. There is no evidence that the donor somatic cell returns to an embryonic state for development into a live born animal.

Nuclear swelling, complete nucleic acid and cellular division is not sufficient to produce a viable embryo. Collas, using MII bovine oocytes as recipient and bovine granulosa cells as donor, viable embryos were not produced as evidenced by the lack of term development (page 266, col. l, lines 1-5). Collas inherently obtained the three criteria of applicant, but failed to obtain bovines. Further, Collas states, citing DiBerardino, adult NT frogs were only obtained from embryonic or larval nuclei, not somatic nuclei (Collas, page 266, col. 1, parag. 2, lines 6-9). Thus, applicant's method seems, from the art, not to be sufficient for term birth.

Applicant has not provided any support for the argument that DNA replication is evidence of demethylation of the genome that is reprogramming of the genome. DNA methylation regulates gene expression and imprints cells so a liver cell expresses a different set of genes than a lung cell (Li, page 5, col. 1, lines 1-12). However, cells replicate without removing the methylation sites, in fact, methylation increases at replication (Li, page 5, col. 3, parag. 1, lines 1-6). Further, Collas demonstrated embryo formation, but there were no live born bovines. This is a clear indication that reprogramming is not always indicated by nuclear swelling, nuclear membrane breakdown, and DNA replication.

Claims 97, 98 and 100 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons set forth in the office mailed August 2, 2007. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 97, 98 and 100 are to a method for cloning a non-human animal from a somatic cell nucleus. However, at the time of filing the art recognized that nuclear transfer or cloning to produce a term animal was unpredictable. Even if applicant's method results in a reprogrammed somatic cell nucleus, it is documented in the arena of nuclear transfer/cloning that pregnancy does not necessarily mean live births.

Applicant argues their method involves contacting a somatic nucleus with an MII oocyte cytoplasm followed by contacting the nucleus with an activated egg cytoplasm, which resulted in nuclear swelling, complete nucleic acid replication and entry into mitosis. Applicant argues this is sufficient to indicate formation of a multicellular embryo by applicant's method. Applicant argues nuclear transfer is art accepted as an inefficient process, and is not unpredictable within the context 35 U.S.C. § 112. Applicant argues the art of Sullivan et al, Polejaeva et al, Betthauser et al, and Chesne et al support the claimed invention resulting in live-born mammals. These arguments are not persuasive.

Polejaeva et al, Betthauser et al, and Chesne et al each performed exposure to intact eggs by inserting the donor somatic cell nucleus into an MII arrested oocyte followed by activation of the oocyte. However, there is no extract involved in any of Polejaeva et al, Betthauser et al, and Chesne et al; each paper discloses only an intact egg. For reasons set forth here and in previous office actions, the artisan at the time of filing would not have taken the disclosed egg extract to mean intact egg. Further, the specification fully discloses the CSF extract and the activating egg extract to be separate steps (specification,).

Polejaeva et al, Betthauser et al, and Chesne et al do not support applicant's enablement as the presently disclosed invention is materially different and separate from the teaching disclosed in any of these references. Thus, the claims when read in light of the specification are not enabled for incubation in an intact egg.

With regard to Sullivan applicant makes several counter-arguments. Applicant argues Sullivan confirmed remodeling of a somatic cell nucleus in a cell extract and produce live offspring using the methodology of the claims. Sullivan, applicant states, used a reprogramming extract of human cells arrested in MII, and transferred condensed chromatin to an enucleated oocyte prior to activation. As result Sullivan obtained blastocysts, which when transferred to surrogate bovines resulted in term births. Applicant argues the specification demonstrated reprogramming after incubation of a somatic nucleus with an MII egg extract would provide a reasonable expectation of success for an MII extract form MDBK cells (Sullivan). Applicant argues the skilled artisan would expect a cell extract to act as their egg extract since both would have the same factors. Applicant states their CSF extract is an MII extract. These arguments are not persuasive.

An egg or oocyte is arrested in metaphase II of the meiotic cycle. The egg or oocyte waits in MII until fertilization or some other event releases the arrest and the egg or oocyte proceeds into cell division. At the time of filing, the artisan would have not though a somatic cell extract would have remodeling capabilities on the line of an egg or oocyte extract. There is no MII in somatic cell division. Further, there is no CSF in somatic cells, but there is MPF. CSF is crucial according to the specification in the remodeling paradigm. Additionally, the MDBK (bovine not human) cells are not arrested in MII, nor are they capable of initiating the developmental process as an oocyte or an egg.

Applicant argues the results discussed in Hochedlinger were achieved using Xenopus eggs not MII arrested to prepare the extract. This argument is not persuasive.

A review of Hochedlinger and Hansis indicates neither publication discusses the mitotic/meiotic status of the oocytes. This is supported by the teachings of Collas that Xenopus extract did not support production of clone Xenopus.

To reiterate, Campbell states reprogramming can only be indicated by the production of a live offspring (Campbell, page 250, col. 1, parag. 2, lines 1-2). Applicant has not even shown blastocyst development, much less term development.

Claims 87 and 89-98 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons set forth in the office action mailed August 2, 2007. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention as claimed encompasses incubation of a somatic cell nucleus in an intact MII egg followed by incubation in an intact induced egg. However, a review of the specification does not reveal this invention was disclosed.

Applicant argues the skilled artisan at the time of filing would have realized through the examples of reprogramming nuclei by exposure to a CSF MII phase egg extract followed by exposure to S-phase activating egg extract that cytoplasm of intact eggs in these defined states also results in the reprogramming of somatic cell nuclei. Applicant argues the skilled artisan would understand applicant's invention extends to the exposure of somatic cell nuclei to the cytoplasm of MII and S-phase eggs would result in reprogramming of the nuclei. Applicant argues the cytoplasmic extracts prepared from such eggs is the equivalent of cytoplasm in an intact egg. Applicant argues clearly defined the stage of the cell cycle and oocyte cytoplasm required for activation. These arguments are not persuasive.

The contemplation in the specification is that egg extracts either at MII, to produce the CSF extract, or the S-phase, to producing the activating extract, is required to cause chromatin condensation and nuclear membrane breakdown in a somatic cell nucleus, and nucleic acid synthesis. There is at no place contemplation of exposing the somatic cell nucleus to an intact cytoplasm. The clear disclosure is that the eggs must be extracted for the disclosed method. Further, the specification teaches exposure to one extract followed by exposure to the second extract. As there is not contemplation of contact of the somatic cell nucleus with an intact egg cytoplasm, the skilled artisan at the time of the instant invention would not have realized this was applicant's invention.

The presence of particular factors in common with the extract and the egg source is intuitive, but it does not indicate applicant contemplated contact with an intact egg cytoplasm as the invention. It is noted that at each place where the specification discusses the stage of the egg, MII or S-phase, the disclosure teaches to prepare extracts from these eggs. For applicant to have support for the claims as written, there needs to be disclosure that exposure to intact egg cytoplasm is part of the invention. Indeed, the invention as disclosed indicates that applicant's invention is only to contact with egg extracts (specification, page 59, lines 5-9; and page 60, lines 9-10), suggesting to the artisan that either intact egg cytoplasm is inoperable or the extract media is essential for reprogramming somatic cell nuclei. There is no contemplation for incubating donor somatic cell nuclei in an intact egg, only incubation in egg extracts. Applicant cannot claim what they have not contemplated.

The claims are free of the prior art. At the time of filing, the prior art did not teach or suggest methods of nuclear transfer, where the donor nucleus was incubated first in a cytostatic egg extract and second in an activating egg extract.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Deborah Crouch, Ph.D./
Primary Examiner, Art Unit 1632

April 14, 2008